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Three Brothers With Mental and Physical Retardation, Hydrocephalus, Microcephaly, Internal Malformations, Speech Disorder, and Facial Anomalies: Mutchinick Syndrome

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We describe three brothers from a nonconsanguineous family with microcephaly, mental and physical retardation, speech disorder, facial anomalies, and internal hydrocephalus in two of the three affected brothers. The youngest brother died at the age of 5 months. He had situs abdominalis inversus, ASD II, and had been operated for internal hydrocephalus and atresia of the biliary duct. A search in the Oxford Medical Database Dysmorphology Program suggested phenotypic similarities with two sisters described in 1972 by Osvaldo Mutchinick in Argentina. Although differences in their phenotypes exist, it is possible that the two sets of sibs represent the same, rare syndrome. This interpretation is supported by the origin of both families from the same geographic region. Am. J. Med. Genet. 73:210–216, 1997. © 1997 Wiley-Liss, Inc.

KEY WORDS: physical and mental retardation; facial anomalies; internal hydrocephalus; ASD II; situs abdominalis inversus; biliary duct atresia

INTRODUCTION

In 1972, Mutchinick described two sisters from Buenos Aires, Argentina, with mental retardation, speech disorder, characteristic facial anomalies, and different organ malformations [Mutchinick, 1972]. The sisters' parents were double cousins once removed. We examined two brothers from the Ruhr area in Germany with a similar phenotype. A third brother with multiple malformations had died in infancy. The similarities between the phenotypes were suggested by a search in the Oxford Medical Database, London Dysmorphology Database [Winter and Baraitser, 1996]. We contacted Dr. Osvaldo Mutchinick and compared our findings. We agreed that the two sib pairs represent a similar, previously unrecognized disorder. To our surprise, the families of the two sib pairs from Argentina and from Germany, now living some 12,000 km apart, originated from the same geographic region in Poland about 50–60 and 100–150 km apart. The family living in Germany was ascertained when we were consulted to evaluate the possible causes for the physical and mental retardation of three of their sons.

CLINICAL REPORTS

The two brothers, patient 1 (Mat.K, VI-2), born December 15, 1984, and patient 2 (M.K., VI-4), born October 6, 1988, were examined in July 1995 and again in September 1996. There was limited information on the condition of the third brother, patient 3 (S.K., VI-5), born June 9, 1993 and deceased November 11, 1993. The sibs' mother reported a daily nicotine consumption of about seven cigarettes during the first four, but not the fifth, pregnancies and denied the use of alcohol or drugs during any of her pregnancies.

Patient 1

Mat. K. (VI-2). The pregnancy with this male fetus was uneventful until in the 32nd week of gestation microcephaly was noted ultrasonographically. The child was born spontaneously with frontal presentation in the 37th week of gestation and the following measurements: 2,540 g (−1.2 SD), 47 cm (−1.4 SD), and head circumference (OFC) 30.5 cm (−1.4 SD). OFC remained below the 3rd centile during postnatal development. The boy's physical and intellectual development also proved severely retarded. He sat at 9 to 10 months, walked at about 2 years, and was toilet trained at 5 years. He spoke simple words at the age of 10 to 11 months and sentences starting at the age of 2 years. He attended kindergarten for retarded children starting at

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the age of 5 and a similar school starting at the age of 6 years. His IQ was reported between 75 and 95. The EEG showed minimal abnormalities during the presleep period. There were presumptive petit mal seizures with clouding of consciousness at the age of about 5 years. He was briefly treated with anticonvulsive drugs.

The child was never seriously ill. Results of hearing tests were normal. The ophthalmologist noted divergent strabismus and a −1.5 D myopia. Corrective lenses were prescribed. He was examined repeatedly in neuropediatric clinic without attaining a diagnosis. His abilities in visual and acoustic perception and social contacts were found about normal. However, language, manual skills, and body control appeared markedly below average. At the age of 10 7/12 years he attended a school for the mentally retarded where he seemed to get along well and established good social contacts and independence. His sense of orientation was reported to be weak. Toilet training and other essential functions presented no problems.

At our first examination, he appeared as a cooperative, very slender, friendly boy. His height was 142 cm (−0.4 SD) and OFC was 48 cm (−3.7 SD). The following clinical abnormalities were noted: hypotelorism with bilateral ptosis, more pronounced on the right lid, corrective lenses for myopia, prominent nose with wide and high nasal bridge, large mouth, thin upper lip, dental malocclusion, poor, irregularly positioned teeth with numerous deficiencies, incisors with rippled irregular ridges, high arched palate, protruding, abnormally modelled low-set ears, high forehead (Fig. 1a–d), and pads on fingers and toes. The karyotype was normal 46,XY.

At the time of his second presentation in our genetics clinic in September 1996, he was 11 9/12 years old. Except for frequent upper respiratory infections and treatment for pes planus, he had an uneventful year. His education has focused on the development of manual skills and of sports. Puberty has started. He is reliable and helpful at home. His speech is still blurred. His vocabulary is adequate as far as can be tested. During the past year, he had no seizures or petit mal episodes. Height was 152.4 cm (+0.6 SD), weight was 40.8 kg (mean), and OFC 49.5 was (−2.8 SD). Inner canthal distance 2.6 cm (−2 SD), outer canthal distance was 7.8 cm (−5 SD), and interpupillary distance was 5.0 cm (10th centile). Ears were 5.7 cm (mean) (Fig. 1a–d).

Patient 2

M.K. (VI-4). The pregnancy with this male fetus was uneventful until hydrocephalus was diagnosed ultrasonographically in the 33rd week of gestation. In the 37th week, the pregnancy was terminated by cesarian section because of hydrocephalus. Birth weight was 2,240 g (−1.9 SD), length was 45 cm (−2.3 SD), and OFC was 37.7 cm (+3.8 SD). The Apgar scores were 9/10. About 2 weeks after delivery, the internal hydrocephalus was corrected by a ventriculo-peritoneal shunt. The infant's postnatal development was markedly delayed. He turned over at 6 months, sat at the age of 12 to 13 months, and walked at 24 months. He spoke simple words at 9 months and simple sentences at 4 years. At 6 9/12 years, he was not yet toilet trained and had severe speech deficiency. Ear and eye functions were normal, except for convergent strabismus and the need for corrective lenses. He attended a regular kindergarten, with good social contacts. In June 1995, a child psychiatrist diagnosed him a former small-for-date baby, mentally retarded with corrected internal hydrocephalus, microcephaly, retarded physical development, speech impairment, myopia, but no signs of childhood autism.

At our examination, he presented as a friendly, very cooperative 6 9/12 year old child with a height of 112 cm (−2.2 SD), weight of 16.5 kg, and an OFC of 50 cm (−1.5 SD). He had considerable speech limitations, a tendency to perseverate, but seemed to understand and follow simple demands. He assumed a forward-bent posture, and his gait was insecure. His face was similar to that of his brother Mat. K.

The following clinical signs were noted: Ptosis of both eyelids, large, protruding, low-set, and abnormally modelled ears, broad and prominent nasal bridge, large mouth, thin upper lip, very poor carious teeth (the front teeth had been extracted because of caries), high, arched palate, high forehead, frontal whorl, and the condition after ventriculo-peritoneal shunt operation without apparent complications, with moderate degree pectus excavatum. His karyotype was normal 46,XY.

At his second presentation in our genetics clinic in September 1996, he was almost 8 years old. He has been attending the low grade of a school for the mentally retarded. He likes music, singing, and drums. His language abilities have not developed further. He was not ill during the past year and he had no seizures. In May 1996, the hydrocephalus shunt system had to be replaced. He had fallen apathetic and the shunt seemed to fail. He appeared not to have progressed physically or mentally since his previous visit 14 months ago. His height was 118.4 cm (−2.0 SD), weight was 20.2 kg, and OFC 50 cm (−1.7 SD) (Fig. 2a–c).

Patient 3

S.K. (VI-5). Only limited information was available on the fifth child in the family who died at the age of about 5 months. The hydrocephalus was noted ultrasonically shortly before birth. Delivery was normal. A ventriculo-peritoneal shunt operation was performed 9 days after birth. The dystrophic child presented with the following internal organ malformations: hydrocephalus internus with marked enlargement of the lateral ventricles, brain tissue defects and increased intracranial pressure, situs inversus abdominalis, intrahepatic atresia of biliary duct, atrial septum defect (ASD II) with left-right shunt and pulmonary stress, partial aplasia of corpus callosum, and hypospadias. Except for situs inversus, spleen, liver, and kidneys were normal. At 2 months, a Kasai operation was performed (hepato-porto jejunostomy). The intrahepatic bile ducts were fibrotic and not functioning. Gallbladder and bile ducts functioned normally. Several operations followed because of malfunctions of the ventriculo-peritoneal shunt due to hemorrhagic hy-

Fig. 1. Patient 1, Mat. K. (VI-2) at the age of 4 3/4 **(a),** 10 7/12 years **(b),** and 11 3/4 years **(c,d).**

TABLE I. Comparison of the Clinical Phenotypes Observed in All Five Children Reported*

	This report			Mutchinick [1972]	
Patients	Mat. K. VI-2	M.K. VI-4	S.K. (VI-5)[a]	IV-1	IV-3
Trait					
Prenatal development					
Microcephaly	+	+	n.r.	+	+
Hydrocephalus	−	+	+	−	−
Postnatal development					
Failure to thrive	−	+	+	+	+
Perinatal feeding difficulties	−	n.r.	+	+	?
Microcephaly	+	+	+	+	+
Hydrocephalus internus	−	+	+	−	−
Delayed milestones	+	+	(+)	+	+
Delayed speech development	+	+	n.r.	+	+
Minor anomalies					
Hypertelorism	−	−	*	+	+
High forehead	+	+	*	+	+
Ptosis	+	+	*	+	−
Antimongoloid palpebral fissures	+	+	*	+	+
Long curly eyelashes	−	−	*	+	+
Myopia	+	+	*	−	−
Light blue iris	+	+	*	+	+
Frontal whorl	−	+	*	−	−
Blond hair	+	(+)	*	+	+
Prominent nose and nasal bridge	+	+	*	+	+
Large mouth	+	+	*	+	+
Thin upper lip	+	+	*	+	+
High arched palate	(+)	(+)	*	+	+
Dental malocclusion	+	+	*	+	−
Frequent caries	−	+	*	−	−
Irregular ridges on incisors	+	−	*	−	−
Large, protruding low-set, dysplastic ears	+	+	*	+	+
Prognathism	+	+	*	+	+
Pectus excavatum	−	+	*	Carinatum	−
Hyperextensible joints	(+)	(+)	*	−	−
Finger, toe pads	+	−	*	−	−
Hyperconvex thumb nails	−	−	*	+	−
Clinodactyly (5th finger)	−	−	*	+	−
Skin, moles	(+)	−	*	+	−
Internal organs					
Partial agenesis of corpus callosum	−	−	+	−	−
Heart murmur	−	−	+	+	−
ASDII	−	−	+	−	−
Biliary duct atresia	−	−	+	−	−
Cuboid shaped dorsolumbar vertebral bodies	−	−	−	+	+
Bilateral renal calyceal dilation	−	−	−	−	+
Rotated kidney	−	−	−	−	+
Situs abdominalis inversus	−	−	+	−	−
Genua valga, pedes valgae	+	−	−	−	+
Hypospadias	−	−	+	Females	
Spastic, insecure gait	−	+	−	+	+
Cytogenetic findings	Normal	Normal		Normal	Normal
Parents					
Consanguinity	−	−	−	+	+
X-ray exposure, maternal	−	−	−	−	+
Nicotine during gestation	+	+	−	−	−

*n.r., not reported. ASD, Atrial septum defect, functional left-right shunt.
[a]Facial and other possible dysmorphisms could not reliably be assessed in patient 3.

drocephalus or bacterial infections. Eventually, a ventriculo-atrial shunt was installed because of hydrocephalus with ventricular enlargement. After surgery, the child developed meningitis, malnutrition, septicemia, microembolisms, and died a few weeks later. Permission for autopsy was denied.

Pedigree and Family History

The pedigree of several generations of ancestors of the brothers showed no evidence for consanguinity of the paternal and maternal families (Fig. 3a) and no record of known genetic or other severe diseases. The

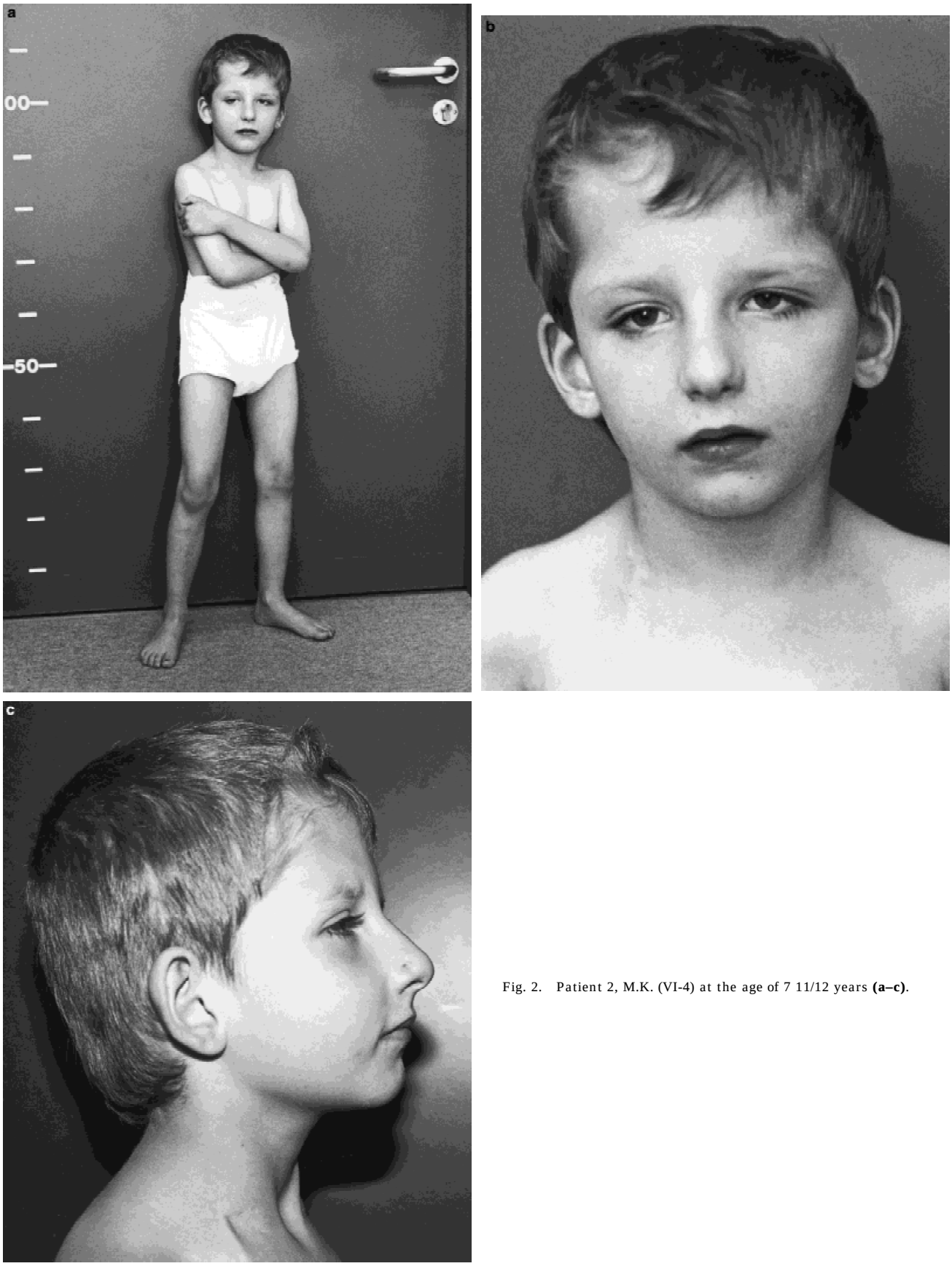

Fig. 2. Patient 2, M.K. (VI-4) at the age of 7 11/12 years **(a–c)**.

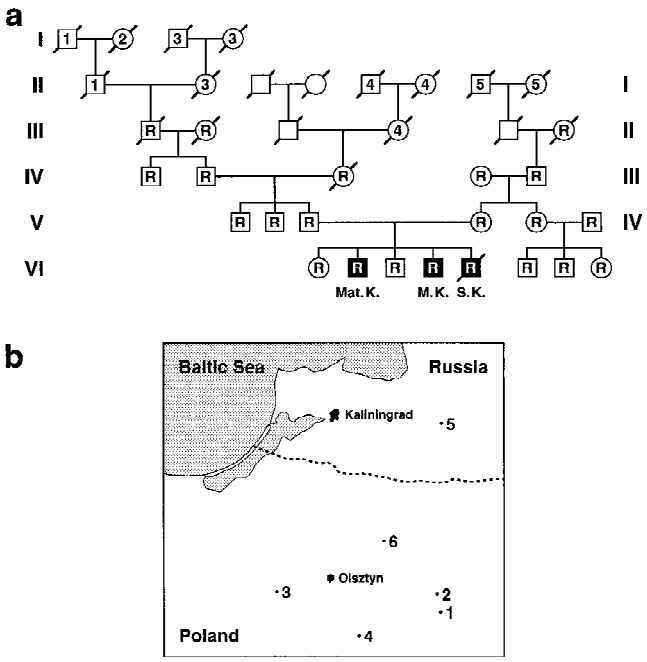

Fig. 3. Origins of the families reported here and by Mutchinick. **a:** Pedigree of the family in Gelsenkirchen, Germany. Symbols inside squares and circles refer to the geographic origins of individual relatives. R, Ruhr area, Germany; 1–6, see (b). **b:** Map of the former Ostpreussen with the towns of possible origins of the families described here and by Mutchinick [1972]. 1, Krzyzè (Kreuzofen); 2, Ukta; 3, Ostróda (Osterode); 4, Malga; 5, Saalan (Stoktinnen, Klein-Waldeck); 6, Kolno (Gross-Köllen). Olsztyn (Allenstein), Kaliningrad (Königsberg).

brothers' parents grew up in the Ruhr area. Several generations ago, both families had moved there from Ostpreussen (East Prussia). The locations of many of the small home towns of family members in the pedigree of Figure 3a are presented in Figure 3b. The brothers' maternal family originated from an area close to Kaliningrad (Königsberg), since 1945 part of Russia. On the paternal side, all ancestors have lived several generations ago (Fig. 3a) in small towns in the Southern part of East Prussia, since 1945 part of Poland. The children's parental families were thus separated by about 150 km.

Of the five children, one girl and four brothers, born to the German family between 1983 and 1993, two had developed normally and were in good health. The healthy sibs were not examined. Three brothers were severely affected as detailed above. The children's mother underwent sterilization in 1993.

Geographic Origins of the Families

In the report published by Mutchinick [1972], the origin of the Argentinean family was cited as Köllen, which is now named Kolno situated in Poland about 85 km south/south east of Kaliningrad (Königsberg) (Fig. 3b, number 6 on the map). In the legend to Figure 3b, geographic names are presented in Polish and in German, since the pre-world war records of the maternal and paternal families give the names of all towns in German.

The family from the Ruhr area reported here has detailed family records on the paternal and maternal sides of the five sibs and could be traced back six and five generations, respectively. As is apparent from the pedigree in Figure 3a, the father's family originated four generations ago from the Southern part of the former East Prussia: Krzyzè (Kreuzofen), Ukta, and Ostróda (Osterode), now located in Poland (Fig. 3b). Starting with generation III on the paternal side, all relatives were born in the Ruhr area (R in Fig. 3a; Herten and Gelsenkirchen). On the children's mother's side, in generations III, IV, and partly II, relatives were born in the Ruhr area (Essen and Gelsenkirchen); earlier generations came from the northern, now Russian, part of the former East Prussia: Stiktinnen and Klein-Waldeck located close to Saalan (Fig. 3b, number 5) East of Kaliningrad.

The map in Figure 3b demonstrates that the origins of the Buenos Aires (Gross-Köllen = Kolno; 6 in Fig. 3b) and of the Gelsenkirchen families are located in small towns situated at distances of less than 50 km (Köllen to Ukta, Kreuzofen, Malga) or less than about 80 km apart (Köllen to Stoktinnen, Klein-Waldeck). However, no family relationships between the Gelsenkirchen and Buenos Aires pedigrees have so far been established.

Comparison of Patients' Phenotypes

Table I compares the clinical phenotypes of the two Argentinean sisters (IV-1 and IV-2) reported by Mutchinick [1972] and of the two brothers examined here (Mat. K., VI-2, and M.K., VI-4). We have also included data on the third brother (S.K., VI-5). It appears that the two Argentinean sisters are similar to Mat. K., VI-2 (Figs. 1, 4), whereas the phenotype of M.K., VI-4 (Fig. 2) differs in some, though not in the major, phenotypic aspects. With the exception of Mat.K., VI-2, all children had severe internal organ malformations. S.K., VI-5, was most severely affected. We can only speculate to what extent the untimely accidental death due to severe scalding of the younger one of the Argentinean sisters might have been related to her physical and/or mental handicaps.

For comparison, in particular to the facial appearance of Mat. K. (VI-2), photographs of the two sisters described by Mutchinick [1972] are presented in Figure 4. There were remarkable similarities in the facial appearances particularly of Mat. K. and the two Argentinean sisters.

DISCUSSION

The clinical phenotypes of the two Argentinean sisters described by Mutchinick [1972] and the two brothers (Mat. K., VI-2, and M.K., VI-4) reported here show several similarities (Table I). It is difficult to decide whether the third deceased brother (VI-5) with multiple inner organ malformations was also affected by the same disorder. The findings of internal hydrocephalus in M.K., VI-4 and S.K., VI-5, has not been observed in the two Argentinean sisters. The most striking facial similarities exist between the two sisters (IV-1 and IV-3) and Mat. K., VI-2, and to a certain extent also to M.K., VI-4. With the exception of Mat. K., all children presented in part with severe internal or-

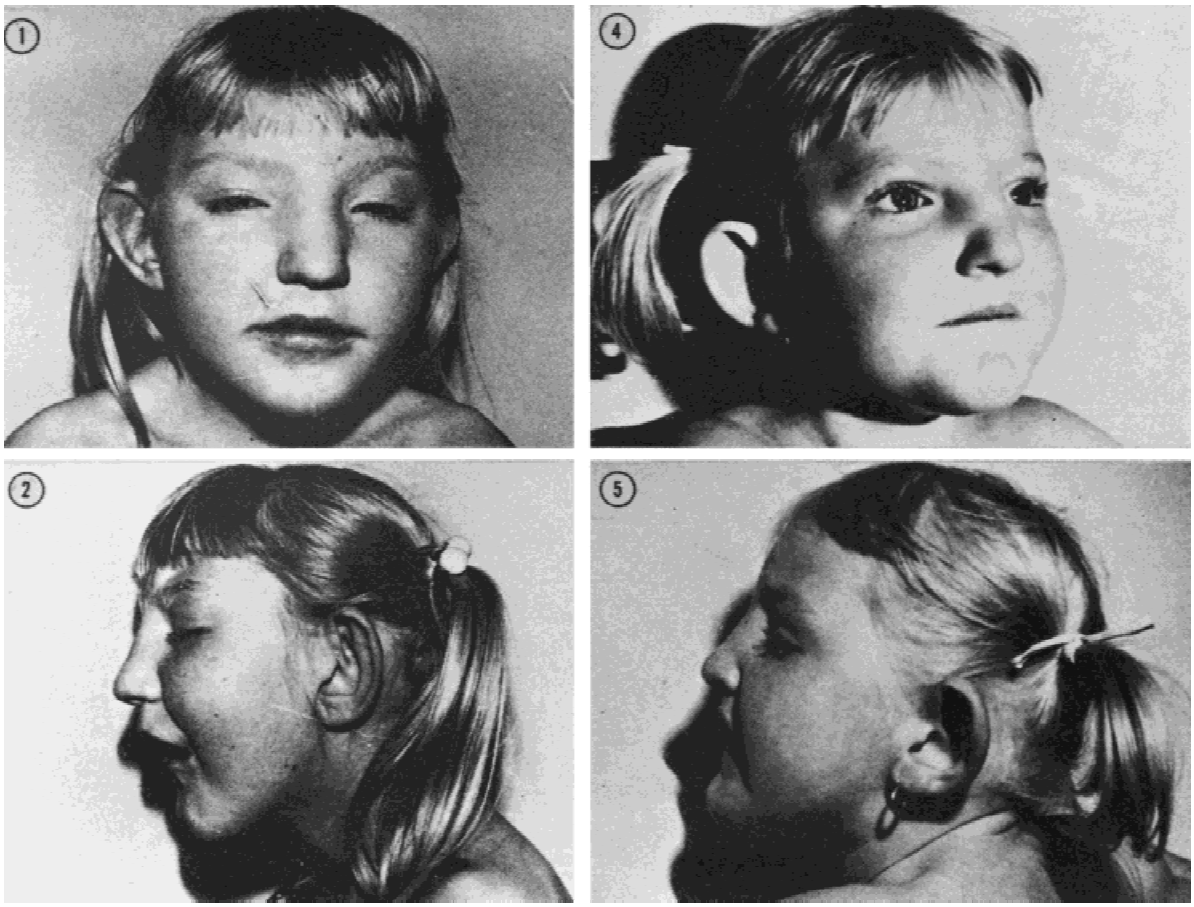

Fig. 4. Photographs of the sisters described by Mutchinick [1972; Reproduced with permission]. 1,2, IV-1 at 7 1/2 years. 4,5, IV-3 at 3 1/2 years.

gan manifestations. The similar phenotypes suggest that members of the two families represent the same syndrome, although differences exist. Investigations on the family backgrounds of the Argentinean and German pedigrees revealed to our surprise a common geographic origin in the former Ostpreussen. An actual relationship between the families several generations ago is thus conceivable.

Mutchinick [1972] compared his observations to other reports of microcephaly and mental retardation and to known syndromes of true recessive microcephaly or Seckel's bird-headed dwarfism but reached the conclusion that they did not fall under any of these diagnoses. We concur and suggest that the patients described by Mutchinick and by us are similar enough to assign them tentatively to the same category, presumably a new genetic disorder, although dissimilarities exist. A search in the Oxford Medical Database [Winter and Baraitser, 1996] suggested similarities to a presumptive syndrome of Fallot complex, associated with mental and growth retardation [Bindewald et al., 1994]. The facial anomalies and the absence of a Fallot complex renders this diagnosis unlikely.

The pedigree of our family and that reported by Mutchinick [1972] suggests autosomal recessive inheritance, but X-linked inheritance is also possible. We suggest that the two sets of sibs present the same phenotype characterized by microcephaly, high forehead, prominent nose and nasal bridge, large mouth, thin upper lip, dental malocclusion, protruding, low-set, poorly differentiated ears, and prognathism. Delayed mental and physical development, mental retardation, speech impairment, and different malformations of internal organs, particularly in the third brother of the Gelsenkirchen family, constitute additional features in common.

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